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Magnetic Stimulation for the Treatment of Parkinson's  
Disease

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## Introduction

The drug treatment of akinesia and rigidity in Parkinson's disease (PD) currently revolves around dopamine containing medications. PD is typically easy to treat early in the disease, but later the response declines and complications develop. Postural instability associated with gait disorder is usually a very disabling and a less treatable manifestation of PD, and it represents a major contributing factor in progression from mild bilateral disease to wheelchair confinement (Paulson, Stern, 1997).

Transcranial magnetic stimulation (TMS) is a tool that allows non-invasive stimulation of the cerebral cortex. Many researchers have used TMS to understand PD pathophysiology, but only a few researchers have used it in therapeutic trials. In the initial study of drug-free patients, repetitive TMS (rTMS) applied to the primary motor areas, contralateral to the performing hand, shortened the time that drug-free PD patients took to complete the Grooved Pegboard Test (Pascual-Leone et al., 1994a). These results were not reproducible, however (Ghabra et al., 1999). Long-lasting improvement of the UPDRS scores, walking speed and self-assessment scale was again reported recently in drug free PD patients after 5 Hz TMS of leg and hand projections in the motor cortex (Khedr et al, 2003). The reported impressive improvement was 13.9 points of the total UPDRS scores, slight improvement of the scores was reported even after the first TMS session. The authors state that evaluation "...was done blindly without knowing the type of rTMS". Single-pulse focal TMS has shortened the simple reaction time in PD patients (Pascual-Leone et al., 1994b). In a different PD study, rTMS at 1 Hz frequency for 15 minutes increased the velocity of finger tapping (Sommer et al., 1998). Siebner et al. (1999, 2000) found that 5 Hz TMS over the motor cortex improved ballistic movements for 20 minutes and decreased contralateral arm motor scores 1 hour after the TMS session. While some of these studies are encouraging, repetitive TMS (rTMS) cumulative effects were not studied, and it is unclear whether rTMS might have any long-lasting therapeutic effects (weeks or months) in persons with PD who are already receiving optimal available therapy. Intriguingly, recent studies with low frequency rTMS, with large circular coils over the vertex or dorsolateral prefrontal cortex (DLPC) in patients receiving levodopa/carbidopa, reported a relatively long-lasting therapeutic effect (Mally, Stone, 1999; Shimamoto et al., 2001).

The reasons for selecting rTMS frequency and target in these previous studies are unclear. The synergistic effect of rTMS and L-DOPA might be assumed, however, based on this data. Prefrontal rTMS with a circular coil increases dopamine release in the caudate nucleus of healthy humans (Strafella et al., 2002). Recently, the same group reported similar effects on the motor cortex (MC) rTMS (personal communication). Extracellular concentration of dopamine was significantly elevated in response to 20 Hz rTMS in the dorsal hippocampus, the shell of the nucleus accumbens and the dorsal striatum (Keck et al, 2002). rTMS also increased dopamine concentration in rat striatum and hippocampus, and decreased it in the prefrontal cortex (Belmaker and Grisaru, 1998). Long-lasting (months) improvement of Parkinsonian symptoms and increased CSF monoaminergic metabolites were also found after ECT in patients who were receiving L-DOPA medication, further supporting the synergistic assumption (Balldin et al., 1982, Fall et al., 1995). Concentration of dopamine and its metabolites in the prefrontal cortex

were increased because of ECT (Yoshida et al., 1998). "Maintenance" ECT has been proposed for the treatment of PD (Aarsland et al., 1997; Fall et al., 1995, 1999).

## **Body**

The first patient was enrolled in the study on December 11, 2002, when the FDA and US Army IRB finally approved the study protocol. Twenty (20) patients with Parkinson's disease have been recruited into the study. Patients' ages ranged from 52 to 81 years. The duration of the disease varied from 7 to 25 years. Nine (9) subjects were randomly included in the real TMS group. In eight (8) the study has been completed. This included Parkinsonian symptom evaluation for one month after the end of the rTMS sessions. One (1) patient was excluded (see adverse effects).

Of the nine (9) patients included in the placebo group, eight (8) completed the study. One (1) of the patients in the placebo group withdrew from the protocol after three (3) rTMS sessions (see adverse effects).

Two (2) of the patients recruited for the study, after signing the consent form and undergoing initial testing according to the protocol (neurological examination, rating with UPDRS, serial reaction test time (SRTT), decided to withdraw from the study. These patients were not randomized, and no TMS sessions were performed.

**Summary of anticipated and unanticipated adverse effects:** The results of 65 real rTMS sessions and 67 placebo rTMS sessions can be analyzed from the point of view of the safety of the magnetic stimulations in PD. One (1) of the patients in the rTMS group was excluded from the study after the first rTMS session because 100% of the motor threshold rTMS was painful to her (minor side effect, anticipated adverse effect). One (1) of the patients in the placebo group withdrew from the protocol after three (3) rTMS sessions because he considered the natural variation of his Parkinsonian symptoms to be the result of the experimental treatment (minor side effect, anticipated adverse effect). No new risks were found based on our results or from other publications.

**Methods:** The rTMS parameters were 100% motor threshold 25 Hz rTMS. Eight patients received all TMS sessions in each of two groups (real rTMS and placebo). Eight rTMS sessions were performed over a four-week period. Four cortical targets were stimulated in each of the sessions (left and right primary motor and dorsolateral prefrontal cortex) with 300 pulses each using Neotonus Neopulse® magnetic stimulator with the solid core coil. For sham stimulation, the procedure was identical to the active condition, but the coil was positioned with its back (inactive) surface touching the scalp. Medication regime remained unchanged during the period of the study. TMS was administered in the beginning of the "on" period after the subject had taken the combination of Sinemet plus one of dopamine agonists (75 min after medication).

To assess balance and gait, time was taken to walk 10 meter distance. A complex movement test was used to measure upper limb bradykinesia. The tests were administered just before and just after each rTMS session, and at the same time interval after L-DOPA medication. Rigidity and tremor were also rated at the same time. Patients received training on the tasks in order to

minimize the effect of learning during consecutive rTMS sessions. UPDRS, SRTT were performed before, after, and one month after the course of TMS treatment (during the same visit). The walk test and complex hand movements test were also done before TMS began (during the first visit), the next day after the end of rTMS course, and one month after the end of rTMS course (8 sessions). The measurements were taken during "on" and "off" periods at the same time of the day and the same time after their medication. To do the walk test, patients were instructed to walk as fast as they could at this point. To do the complex movement test the patients were instructed to do 10 flexion-extension movements in the elbow joint simultaneously squeezing the rubber bulb twice during each flexion-extension cycle.

**Results:** Measurements of balance and gait, and upper limb bradykinesia were done before, after and one month after the course of rTMS treatment during "on" and "off" periods. Repeated measures three way ANOVA with group factor (real rTMS vs. placebo group), date factor (measurements before, after, and 1 month after rTMS, three levels), and "on"/"off" factor (measurements during "on" or "off" period) was done to evaluate balance and gait change after rTMS. Two main effects were found: the date factor ( $F_{2, 26}=27.67$ ;  $p<0.001$ ;  $\epsilon=0.81$ ), and "on"/"off" factor ( $F_{1, 13}=8.66$ ;  $p<0.01$ ;  $\epsilon=1.00$ )\*. Date  $\times$  group interactions was also statistically significant ( $F_{1, 13}=23.25$ ;  $p<0.0001$ ;  $\epsilon=0.81$ ). In the real rTMS group the post-hoc Newman-Keuls test revealed the difference between before and after, before and 1 month after measurements ( $p<0.0001$  for both comparisons). The difference between after and 1 month after measurements was not statistically significant ( $p=0.077$ ) though there was slight decrease in the rTMS effect 1 month after measurement (Fig. 1). There were no statistically significant differences between any measurements in the placebo group.

Fig. 1 demonstrates the decrease of walking time in the real rTMS group over the course of treatment and no change in the placebo group.

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\* Repeated measures analyses of variance (ANOVA) were carried out with the Greenhouse-Geisser correction for inhomogeneity of variance applied where appropriate; reported are the uncorrected degrees of freedom, the epsilon value, and probability level following correction. Newman-Keuls test was used to test the significance of post-hoc comparisons.

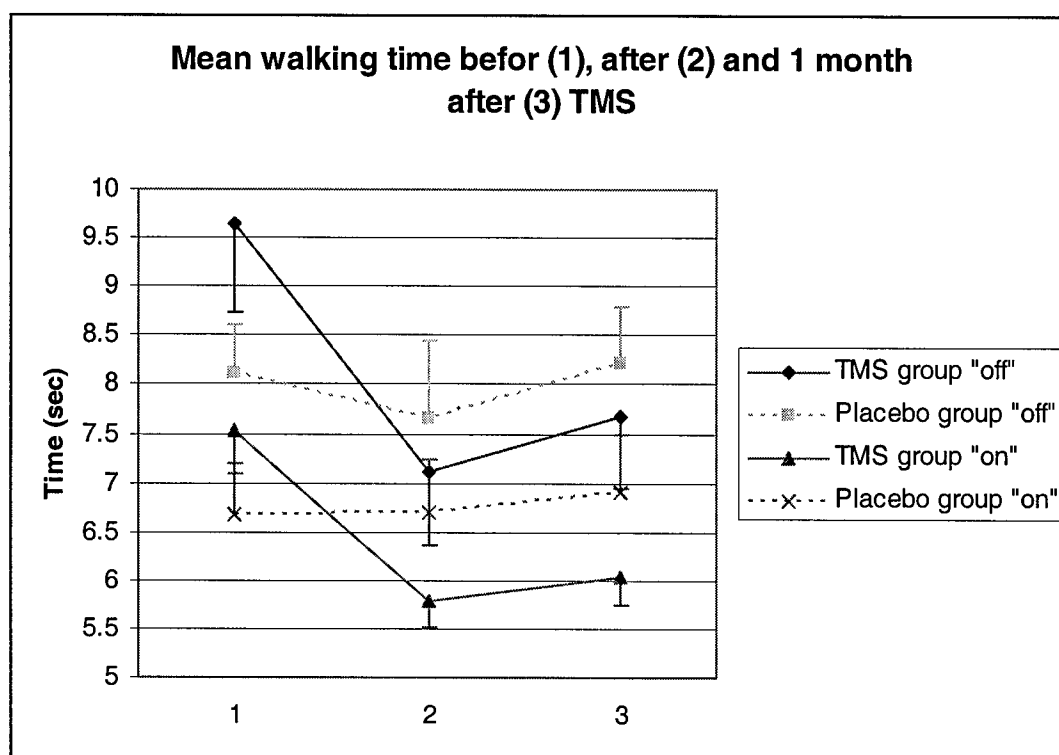


Fig. 1. Time of the 10-meter distance walk before, after and 1 month after rTMS course.

Abscissa – the number of the measurement. Ordinate – time to walk the 10-meter distance.

To evaluate upper limb bradykinesia, we conducted a repeated measures four way ANOVA statistical analysis with factors: group (rTMS vs. placebo), date factor (measurements before, after, and 1 month after rTMS; three levels), “on”/“off” factor (measurements during “on” or “off” period), right/left factor (executing the test by the right or the left hand). Two main effects were found: the time factor ( $F_{2, 26}=37.655$ ;  $p<0.00001$ ;  $\epsilon =0.64$ ) and “on”/“off” factor ( $F_{1, 13}=39.498$ ;  $p<0.00001$ ;  $\epsilon =1.00$ ). In the real rTMS group the post-hoc Newman-Keuls test revealed the statistically significant difference between before and after, before and 1 month after measurements ( $p<0.0001$  for both comparisons). The difference between after and 1 month after measurements was not statistically significant ( $p=0.9456$ ). There were no statistically significant differences between any measurements in the placebo group.

Fig. 2 illustrates that an improvement of the complex hand movements test was a result of rTMS treatment.

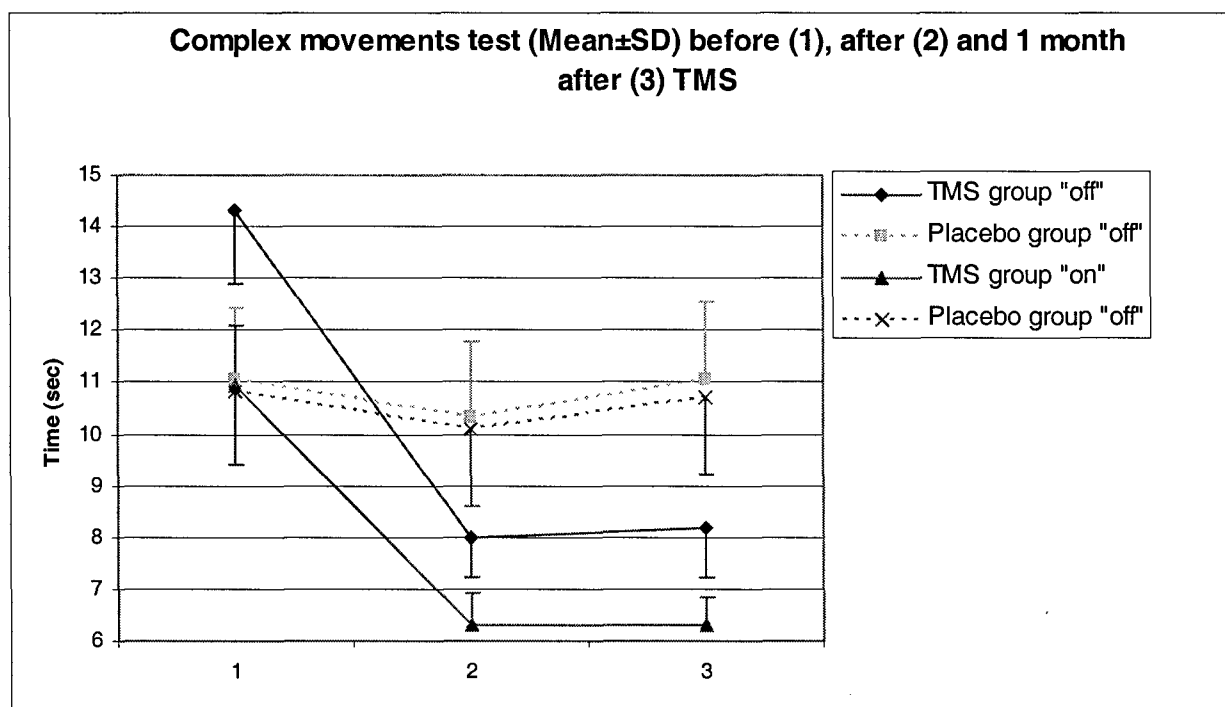


Fig. 2. Time of the complex movement test before, after and 1 month after the TMS.

Abscissa – the number of the measurement. Ordinate – time of execution of the complex movement test. The measurements for the left and right hand, before and after rTMS course are pooled. Each point represents two measurements for each of 8 patients in the group (for right and left hand).

To evaluate rTMS effect on balance and gait over the period of the treatment we conducted a three way repeated measures ANOVA statistical analysis with factors: group (real vs. sham group), session factor (rTMS session number, 8 levels), and before/after factor (before or after rTMS session). A statistically significant session factor was found ( $F_{7, 98}=7.171$ ;  $p<0.001$ ;  $\epsilon=0.35$ ) and group/session interaction ( $(F_{7, 98}=6.300$ ;  $p<0.001$ ;  $\epsilon=0.35$ ). No statistically significant findings were revealed in the placebo group.

To demonstrate an rTMS effect for each group, further analysis with a two way repeated measures ANOVA for each group was done separately. A significant session factor was found in real rTMS group ( $F_{7, 49}=8.207$ ;  $p<0.01$ ;  $\epsilon=0.25$ ). There was no significance of the second factor (before/after) or factors interaction. There were no statistically significant changes in the placebo group.

The averaged results of the 10 meter walk test administered before and after each rTMS session are presented on Fig. 3. Gradual cumulative decrease of the time was observed in patients undergoing the real rTMS, though no obvious slope could be seen in the placebo group over the same time and number of TMS sessions.

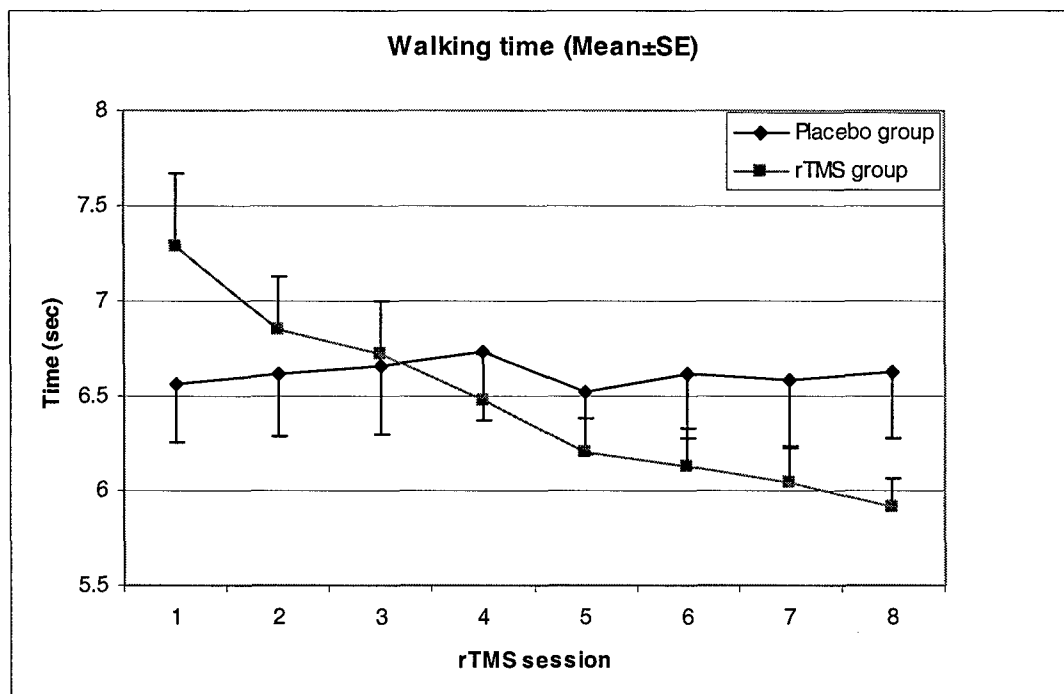


Fig.3. Time of the 10-meter distance walk (averaged data).

Abscissa – number of the rTMS sessions done in each of the patients. Ordinate – time to walk the 10-meter distance. The measurements before and after each rTMS session are pooled. Each point represents two (2) measurements for each of 8 patients in the group (before and after individual rTMS session).

To evaluate rTMS effect upper limbs bradykinesia over the period of the treatment we conducted four way repeated measures ANOVA statistical analysis with factors: group (real vs. sham group), session factor (rTMS session number, 8 levels), and before/after factor (before or after rTMS), hand factor (left or right hand executing the test). Significant session factor was found ( $F_{7, 98}=11.75$ ;  $p<0.0001$ ;  $\epsilon=0.55$ ) and group/session interaction ( $F_{7, 98}=3.59$ ;  $p<0.01$ ;  $\epsilon=0.55$ ). Before/after factor was also significant ( $F_{1, 14}=4.86$ ;  $p<0.05$ ;  $\epsilon=1.00$ ). To demonstrate an rTMS effect for each group, further analysis with a three way repeated measures ANOVA for two groups separately was done. Two main effects were found in the real rTMS group: session factor ( $F_{7, 49}=14.638$ ;  $p<0.0001$ ;  $\epsilon=0.35$ ) and before/after factor ( $F_{1, 7}=7.724$ ;  $p<0.05$ ;  $\epsilon=1.000$ ). There were no statistically significant changes of the combined movement test time in the placebo group.

The results of the complex movements test are summarized in Fig. 4. A gradual cumulative decrease was observed in patients when the real rTMS was applied. Still, some minor slope existed in the placebo group (not confirmed by statistical analysis).

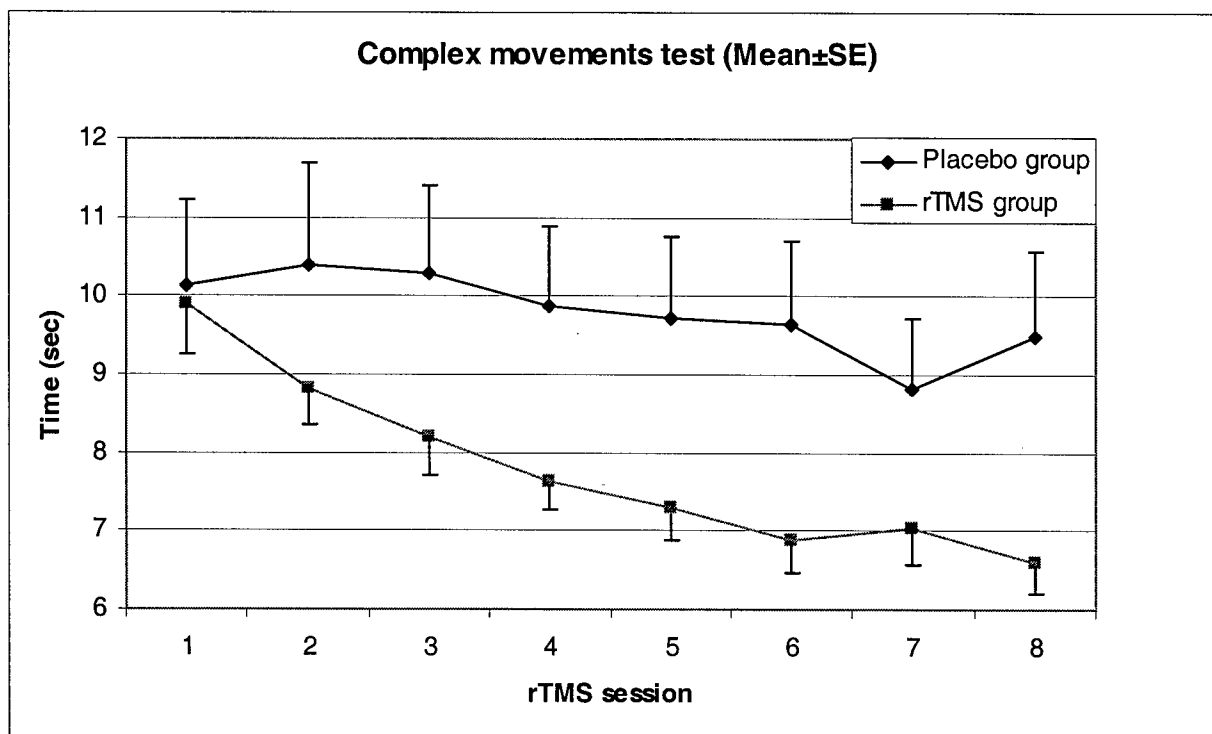


Fig.4. Time of the complex movement test (averaged data).

Abscissa – number of the rTMS sessions done in each of the patients. Ordinate – time of execution of the complex movement test. The measurements for the left and right hand, before and after each rTMS session, are combined. Each point represents four (4) measurements for each of 8 patients in the group (before and after individual rTMS session, left and right hand).

Thus, real rTMS resulted in gradual cumulative improvement of balance and gait which was the primary end point of this study, as well as in more pronounced improvement of the complex combined hand movements (36% time shortening of the complex movement test vs. 18% in the walking test).

We did not observe clinically improvement of the parkinsonian symptoms as a result of a single rTMS session (while comparing rigidity and tremor before and after individual rTMS session). There was statistically significant difference of the before/after factor in the real rTMS group only (with after rTMS time shorter then before) indicating this might be a single rTMS session effect, since medication was presumably the same in the placebo group. It is difficult to explain this before/after difference by pharmacokinetics alone.

We did not manage to prove statistically the improvement of the UPDRS scores in real rTMS group due to the variability of the parkinsonian symptoms from day to day with only three measurements of the scores (before, immediately after the rTMS course and one month after the rTMS). There were no statistically significant changes of the UPDRS scores in the placebo group. See Table 1, 2 for the motor and total UPDRS scores.

Table 1. UPDRS scores before rTMS, after rTMS and one month after rTMS in real rTMS group.

UPDRS scores (Mean $\pm$ SE)	“off” before	“off” after	“off” 1 month after	“on” before	“on” after	“on” 1 month after
Motor	38.9 $\pm$ 4.9	36.0 $\pm$ 3.7	33.0 $\pm$ 2.6	26.3 $\pm$ 1.7	25.4 $\pm$ 1.9	22.0 $\pm$ 2.9
Total	68 $\pm$ 6.0	64.3 $\pm$ 5.8	60 $\pm$ 5.0	44.0 $\pm$ 2.7	43.9 $\pm$ 4.2	39.9 $\pm$ 3.1

Table 2. UPDRS scores before rTMS, after rTMS and one month after rTMS in the placebo group.

UPDRS scores (Mean $\pm$ SE)	“off” before	“off” after	“off” 1 month after	“on” before	“on” after	“on” 1 month after
Motor	30.0 $\pm$ 2.7	30.7 $\pm$ 4.3	29.4 $\pm$ 3.4	20.3 $\pm$ 4.3	19.4 $\pm$ 3.8	25.4 $\pm$ 3.7
Total	56.9 $\pm$ 4.5	58.3 $\pm$ 6.2	59.3 $\pm$ 6.7	38.0 $\pm$ 4.6	36.1 $\pm$ 3.9	45.9 $\pm$ 6.3

All deviations from the initial investigational plan were reported to the FDA, NINDS IRB, and US Army Research and Materiel Command as amendments before their implementation. These changes in the plan facilitated the process of the recruitment of the patients into the study and were done because of a shortage of available patients. They included the reduction of the minimal L-DOPA dose to 375 mg/day, increase in the minimal time of the 10-meter walking test, payments to patients, advertising in local newspapers, and giving the patients options to be admitted to the Clinical Center for the period of the study. Also, initial and final testing were slightly extended to include the “off” medication period, in comparison to only during the “on” period testing initially.

### Key Research Accomplishments

- Collection of the data defining clinical effects of the rTMS in patients with PD was finished.
- Statistical analysis of the data was done.
- The cumulative improvement of balance and gait, upper extremities bradykinesia after rTMS with proposed parameters and regimen in PD patients on L-DOPA medication was demonstrated. This effect lasted at least one month (the duration of the study).

### Reportable Outcomes

The patient database was developed as a unique part of this study. It includes all experimental data and adverse effects. The purpose of the database is to aid in the storage and analysis of the data.

An abstract: “Placebo-Controlled Study of the Repetitive Transcranial Magnetic Stimulation (rTMS) for the Treatment of Bradykinesia in Parkinson's Disease (PD)” was submitted to the Movement Disorder Society meeting, June 13 - 17, 2004 Rome, Italy

The full-size publication is in preparation.

## Conclusions

rTMS with proposed parameters and regimen is safe in patients with PD. It cumulatively improves balance and gait, and bradykinesia of the upper extremities. The therapeutic effect of the rTMS lasts for at least 1 month after the end of treatment.

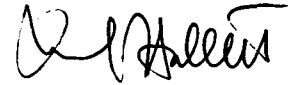
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A handwritten signature in black ink, appearing to read 'Mark Hallett', with a stylized, cursive script.

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